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Dense deposit disease: A variant of membranoproliferative glomerulonephritis

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It has been demonstrated in previous studies that there are several morphological variants of membranoproliferative glomerulonephritis (MPGN) [1–3]. In most cases mesangial cell proliferation and an increase in mesangial matrix are associated with capillary wall thickening ("classical MPGN"). In some cases, in addition to the previous findings, there is an accentuation of lobulation of glomerular tufts due to the presence of sclerotic nodules in most of the centrilobular areas. This is accompanied by peripheral displacement or obliteration of capillary lumens (lobular GN or "MPGN with lobular pattern"). More or less abundant epithelial crescents may be seen in both variants.

However, analysis of the capillary wall thickening by light and electron microscopy reveals two types of involvement: In the first, thickening of the capillary walls is due to an interposition of mesangial matrix between the endothelium and a normal basement membrane, producing a "double contour" appearance. Electron microscopy, as well as immunofluorescence microscopy, reveals in all cases the presence of abnormal subendothelial deposits. This variety is called *MPGN with subendothelial deposits* (*SED*). In the second, the thickening of the capillary walls is due to the presence of an abnormal dense refractile material located in the basement membrane itself. "Double contours" here are an inconstant finding. This variety warrants the name of *MPGN with dense intramembranous deposits* (*DIMD*); it has recently been called *laminal glomerulonephritis* [4].

These two varieties of MPGN are at present not distinguished one from another in most clinical studies because it may be difficult to recognize MPGN with DIMD on light microscopy. Therefore, with one exception [5], there are no extensive studies dealing with this specific entity.

We observed 44 cases of this variety of MPGN and report here detailed clinical and complement studies, together with histological data in these cases for comparison with 84 cases of MPGN with SED seen during the same period of time.

Methods

Out of the 128 renal biopsy specimens studied in our laboratory between 1959 and 1974 and for which the diagnosis of MPGN was established, we found in 44 cases by light or electron microscopy or both the morphologic characteristics of "dense deposit disease". The biopsy specimens were obtained at various stages of the disease (12 days to eight years) (Fig. 1), less than one year after the apparent onset in 26 patients. Repeat biopsies were performed in nine patients and biopsy specimens of the graft kidney were obtained in five.

For *light microscopic* studies, renal biopsy specimens were fixed for 6 to 24 hr in Dubosq-Brasil fluid and, subsequently, for 24 hr in 15% formalin. All the specimens were then embedded in paraffin and cut at 2 to 3 μ. Four stains were used: hematoxylin-eosin, trichrome light green, periodic acid-Schiff with hematoxylin, and silver impregnation according to Wilder.

Electron microscopic studies were performed in 14 patients. Following fixation in osmium tetroxide and postfixation in glutaraldehyde, the specimens were embedded in epoxy resin (Epon) and stained with uranyl acetate and lead citrate. In 12 cases, silver staining methods were used to demonstrate clearly the exact location of the deposits [6].

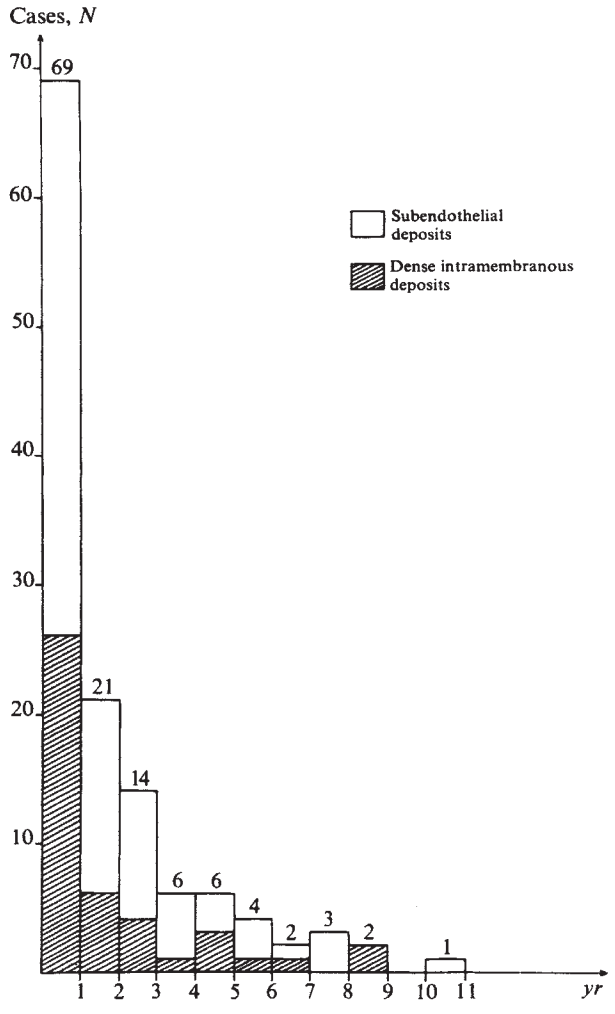

Fig. 1. *Interval between onset and first renal biopsy.*

Immunofluorescence microscopic studies were done in 12 cases. The following sera labeled with fluorescein isothiocyanate were used in all cases: anti-IgG, anti-IgA, anti-IgM, anti-β_1C, antialbumin and antifibrinogen (Hyland Laboratories). Anti-C1q serum was used in five cases, anti-C4 in five, and antiproperdin in four.

The C3 *component of complement* was measured in the plasma of 23 patients, the C4 component of complement in 20 and the C3 PA (GBG) in 17 by the radial diffusion method using commercially available immunoplates (Hyland: C3, Behringwerke Laboratories: C4 and C3 PA).

The mean normal concentrations (± 2 SD) determined from results of normal children were 122 ± 50 mg/100 ml for C3, 44 ± 21 mg/100 ml for C4 and 25 ± 12 mg/100 ml for C3 PA.

The C1q component of complement was measured in the plasma of 17 patients by the radial diffusion method. The mean normal concentration (± 2 SD) was $98\% \pm 29$.

Clinical observations

The disease affected both sexes equally (24 girls and 20 boys). Symptoms never occurred before the age of 4 yr and most patients were more than 8 yr old at the onset (Fig. 2).

The appearance of urinary symptoms was preceded by an acute infection in 23 patients (Fig. 3): sore throat in 20 cases with an increase in ASO titer (>400 units) in 9 of these, meningococcal meningitis in 1 case and unexplained fever in 2 cases. A partial lipodystrophy was associated with the nephropathy in three patients. Determinations for systemic lupus erythematosus were negative in all the patients who were tested.

The presenting symptoms were edema in 17 children and macroscopic hematuria in 16. In the remaining 11 patients, proteinuria was discovered by routine urinalysis (Fig. 4). All patients had proteinuria, which was accompanied by a nephrotic syndrome in 37. The nephrotic syndrome was persistent during the entire course of the disease in 24 patients and transient in 13 others. Seven children never had a nephrotic syndrome (Fig. 4). In all patients but one, proteinuria was associated with hematuria which was macroscopic in 23 of them, mainly during the course of the first year of the disease. Two patients, both with lipodystrophy, had recurrent episodes of macroscopic hematuria after the first year of the disease.

Eleven patients had hypertension at onset which was

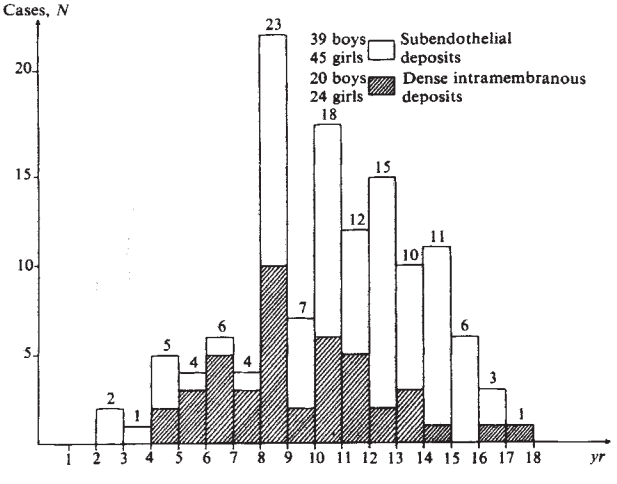

Fig. 2. *Age at onset.*

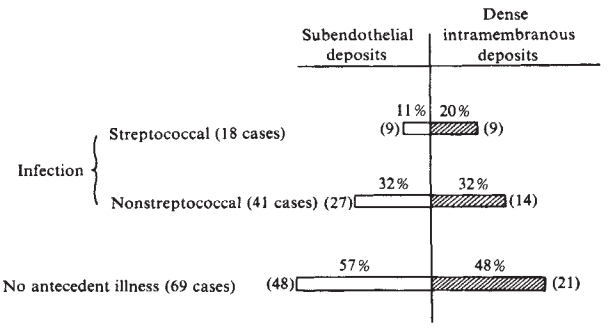

Fig. 3. *Etiology.*

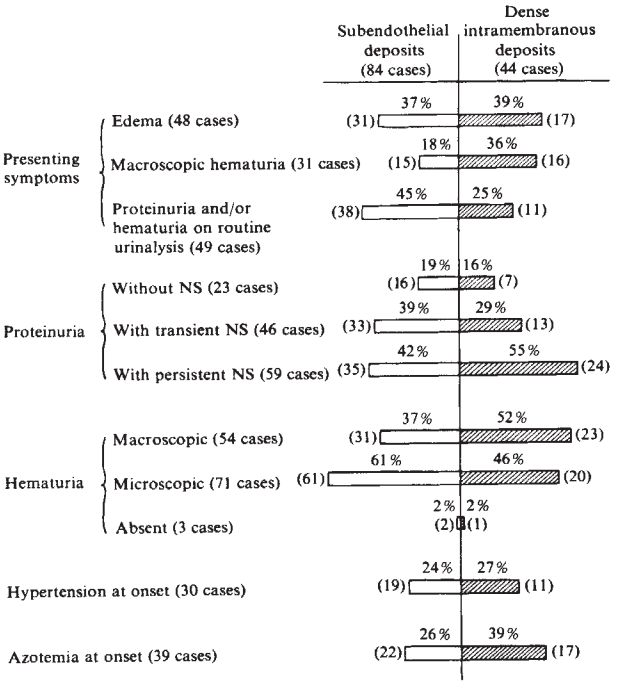

Fig. 4. *Clinical symptoms of membranoproliferative glomerulonephritis (MPGN).*

transient in all but two (Fig. 4). Seventeen patients presented with renal insufficiency at onset, and in four others, azotemia appeared within a few weeks. Of the 21 patients in which the glomerular filtration rate (GFR) was decreased, 10 had a rapidly progressive course and developed terminal renal failure within 3 to 20 months. (Renal biopsy revealed diffuse epithelial crescents in all.) In five patients the evolution towards a terminal stage was slower (two years, six months to ten years, three months). The six remaining patients recovered from their early episode of renal insufficiency.

Renal insufficiency appeared several months later in three patients and progressed to terminal renal failure within six to seven years.

Five patients were transplanted, with removal of the homolateral kidney. Removal of the second kidney was performed in one patient. Recurrence of the lesion was seen in the five patients whose transplant was biopsied. Three of them developed renal failure which was considered to be due to a severe chronic rejection.

Immunosuppressive therapy (chlorambucil) was administered to 30 patients for a variable period of time and at various stages of the disease with no demonstrable effect.

In three children a disappearance of all symptoms was observed. In two, the remission lasted, respectively, two and three years but was followed by a relapse. One of them died 9 years, two months after onset; the other one is in chronic renal failure after a follow-up of 12 years. The third patient has been in remission for three years, nine months after a course of two years characterized by proteinuria and recurrent macroscopic hematuria.

At the latest evaluation, the status of the 44 patients was as follows (Fig. 5): 18 patients were dead or receiving repetitive hemodialysis; 1 was in chronic renal failure; 24 had persistent proteinuria, associated with a nephrotic syndrome in 11; and 1 has been in complete remission for three years, nine months. For the survivors the period of follow-up was variable: four months to ten years, ten months with a mean of four years, nine months.

The actuarial survival curve (Fig. 6) shows that the 50% statistical mortality occurred in this group of patients in the ninth year.

Morphological study

Light microscopy (Figs. 7 and 8). In all patients lesions affected the majority of glomeruli. The changes consisted of hypertrophy and hypercellularity of the

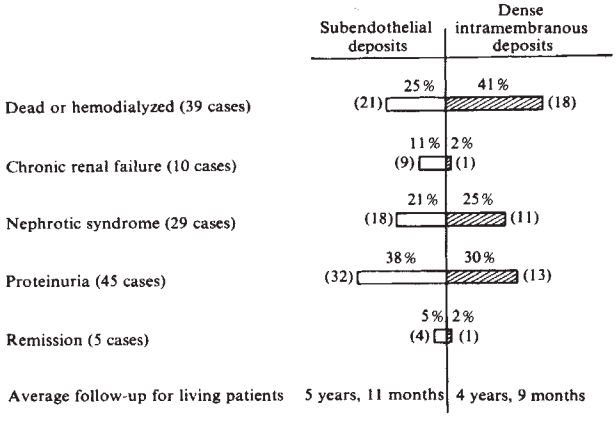

Fig. 5. *Status at last follow-up observation.*

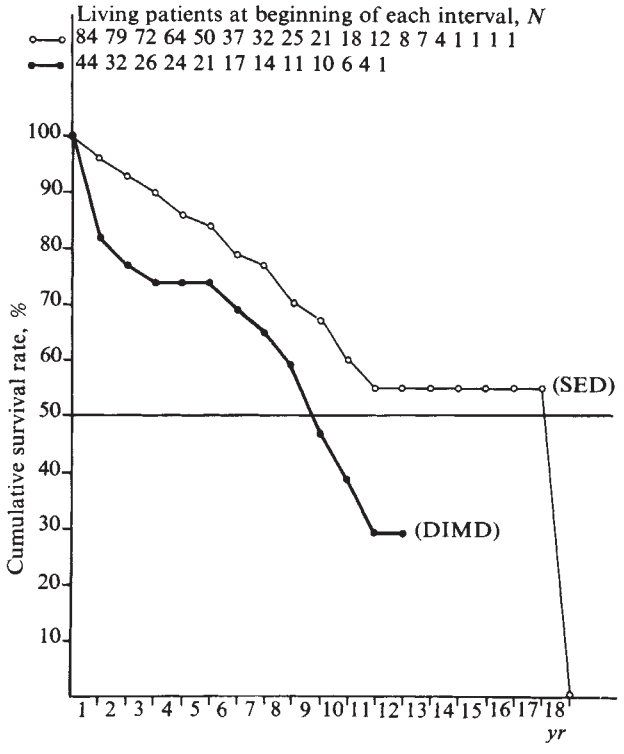

Fig. 6. *Actuarial survival curve.* The 50% statistical mortality occurs between the ninth and tenth years.

tuft, increase in mesangial matrix and thickening of the capillary walls.

The proliferation involved mainly the mesangial cells, and was mild in 11 patients, moderate in 22 and marked in 11. An abnormal number of neutrophils was found in the lumens of some glomerular capillaries in 19 patients. The increase in mesangial matrix was of variable intensity, but in seven patients it was so marked that it formed centrilobular sclerotic nodules which gave a lobulated appearance to the tuft (Fig. 8). In the mesangium of 22 patients, refractile granules of varying size—often colored red by trichrome stains—were present. In one patient there were also curved violaceous deposits in the mesangium. In 13 patients (of whom 2 had a lobular pattern), more or less diffuse epithelial crescents were present in Bowman's space.

In all cases thickening of the glomerular capillary walls was due to the presence of more or less diffuse, dense deposits replacing the basement membrane, which took on a ribbon-like, refractile appearance (Figs. 7 and 8). On silver impregnation the basement membrane itself was thickened by a dense material colored brown. In half of the cases, the presence of segmental "double contours" indicated that peripheral extensions of mesangial matrix were also present. These same "dense deposits" were found focally in Bowman's capsule and tubular basement membranes. It was not rare to find them equally in arteriole walls, in a subendothelial position. In 15 patients, bulky subepithelial deposits ("humps") were seen on the epithelial side of the basement membrane. In two patients, some capillary loops had a hatched appearance similar to that seen in extramembranous glomerulonephritis (subepithelial deposits separated by "spikes").

In the serial biopsy specimens, there were some modifications of the initial pattern. In one case the dense deposits had partly regressed, but in the eight other

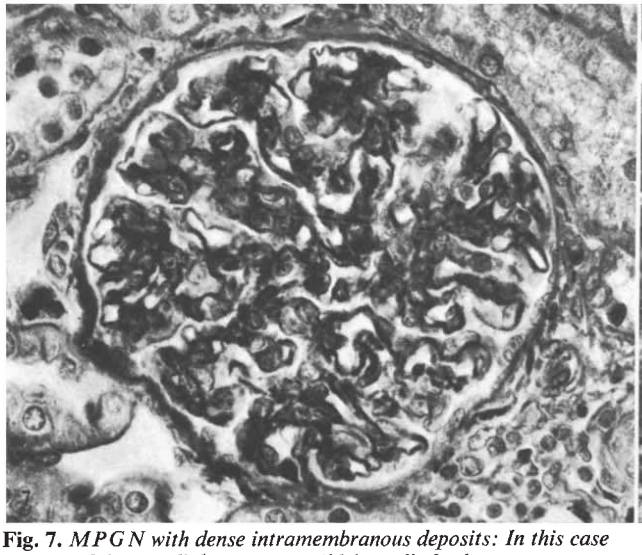

Fig. 7. *MPGN with dense intramembranous deposits: In this case mesangial hypercellularity was mild but all the basement membranes were thickened and refractile (trichrome, × 475).*

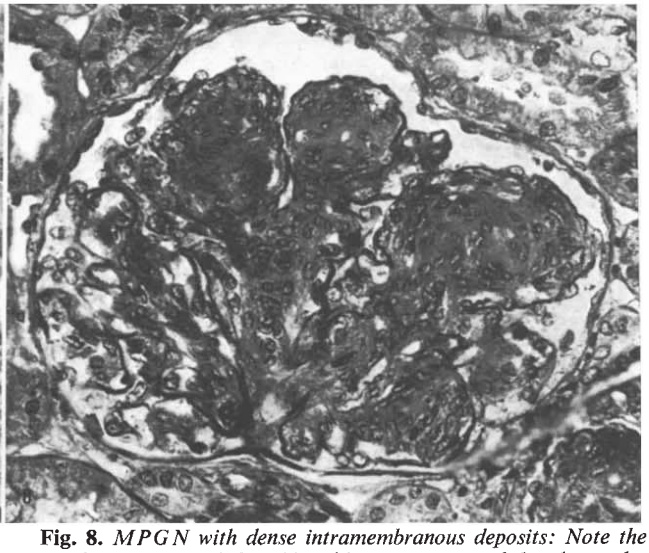

Fig. 8. *MPGN with dense intramembranous deposits: Note the lobular pattern and the ribbon-like appearance of the glomerular basement membranes at the periphery of the lobules as well as in segments of Bowman's capsule (trichrome, × 340).*

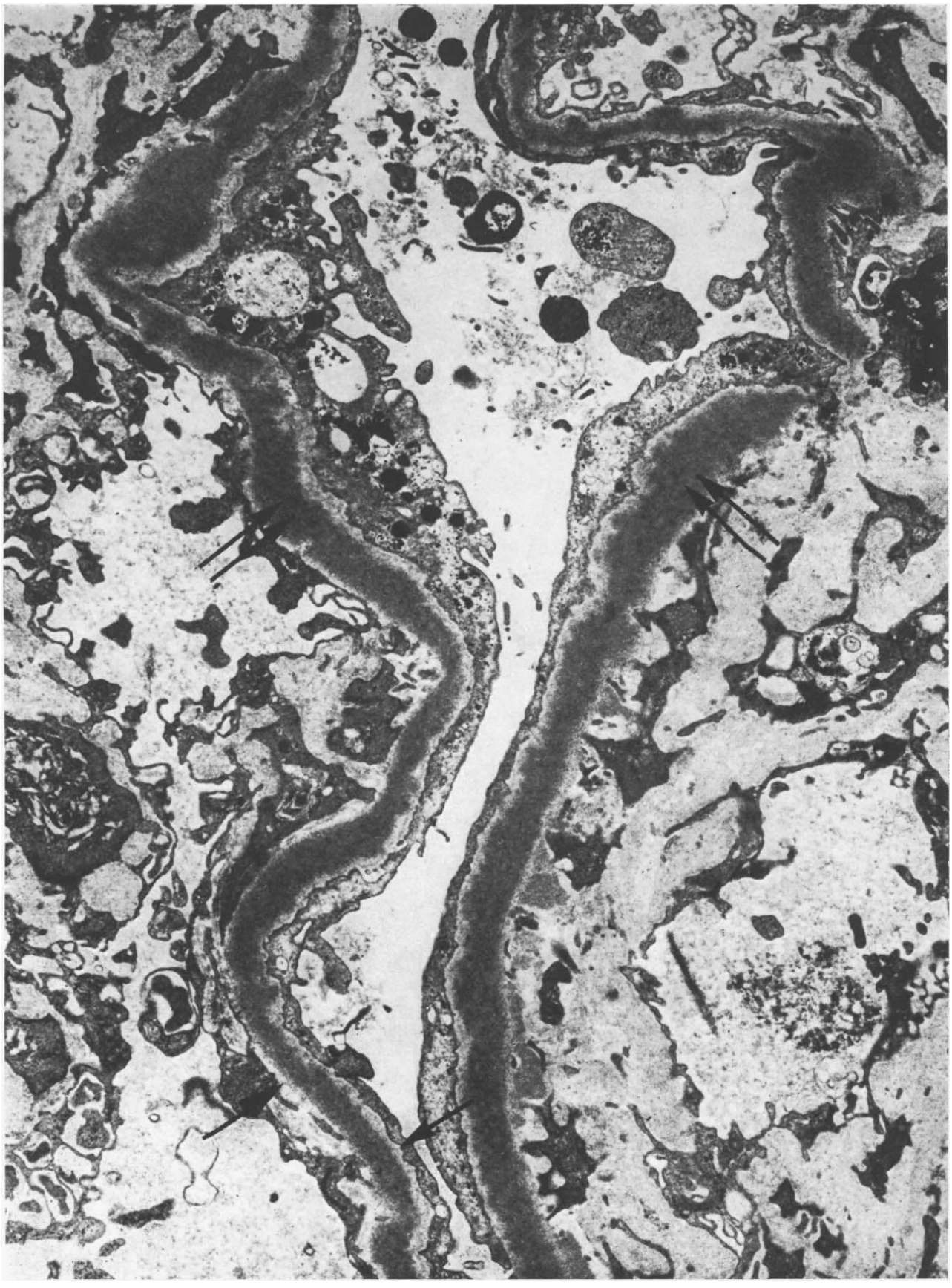

Fig. 9. *MPGN with dense intramembranous deposits: Bands of electron-dense deposits are seen in the midportion of the lamina densa (↗↗) between the two light layers (↗) (uranyl lead; electron micrograph, ×18,000).* Subendothelial mesangial expansions giving a "double contour" appearance reduce the capillary lumen. Note foot-processes fusion.

Fig. 10. *MPGN with dense intramembranous deposits: Discontinuous and segmental intramembranous dense "deposits" are present (silver methenamine; electron micrograph, ×4,500).* The thickening of the basement membrane is predominantly seen next to the mesangial stalk (↗). The abnormal material protrudes towards the internal side of the basement membrane. Note the presence of "humps" (↗ ↗) and of mesangial deposits (↗ ↗ ↗).

specimens the deposits in the basement membranes had clearly increased, and were calcified in the tissue obtained by nephrectomy in two hemodialyzed children. Mesangial proliferation was milder in four patients. An interesting feature was the complete disappearance of the lobular pattern in one patient.

In the specimens of the biopsies performed in the transplanted kidneys, "dense deposits" were found in the glomerular, capsular and tubular basement membranes in all patients although they were very segmental. Mesangial proliferation was always absent.

Electron microscopy. In all glomeruli examined, the constant lesion was the presence of a strongly electron-dense material located in the midportion of the basement membrane, taking the place of and widening the normal lamina densa. When stained by uranyl lead, this abnormal substance appeared homogeneous and much denser than normal lamina densa. It was always well delineated from the mildly electron-dense lamina rara interna and externa. When impregnated by silver methenamine, this material exhibited the same strong affinity for silver as the lamina densa.

The abundance and the diffusion of these dense "deposits" were variable. In 11 patients, the thickening affected the majority of the capillary loops but two different pictures were observed: in six cases, there was a continuous linear distribution of the abnormal material producing a thick dense but regular basement membrane (Fig. 9); in five cases, there was an irregular fusiform swelling of the lamina densa. In these last five cases, silver impregnation best demonstrated the regular external edge of lamina densa and the irregular protrusion of the dense material towards the endothelial cells. The width of the pathological basement membrane usually varied between 5000 and 15,000 Å but it could reach 40,000 Å. In three cases the deposits were very segmental located predominantly in the basement membrane adjacent to the mesangial areas (Fig. 10).

In three cases a few granular, moderately dense deposits were observed on the internal side of the dense basement membrane.

In ten patients, finely granular, moderately dense subepithelial deposits were clearly visible (Fig. 11). They were hump-like and numerous in six cases (Figs. 10 and 11), but rare and predominantly located on the basement membrane adjacent to the mesangial stalks in four. In two of these ten patients, the hump-like deposits were associated in some loops with flat subepithelial deposits which were often separated by very thick and dense spikes. Moreover, in some loops, patchy deposits of weaker density were embedded in the abnormally dense lamina densa mimicking the lesions observed in advanced stages of membranous nephropathy.

Mesangial proliferation was sometimes very marked and accompanied by considerable increase in the mesangial matrix and circumferential interposition of mesangial cells and matrix, giving a "double contour" appearance to the capillary walls. Most often mesangial proliferation was moderate or minimal.

Diffuse mesangial deposits in every stalk were present in all cases. They were exclusively situated along the basement membrane only once. In all the other cases they were predominantly located in the mesangial matrix where they formed round nodules or masses bulging into the basement membrane-like material. They appeared either very dense and homogeneous or moderately dense and finely granular.

In five patients, there were numerous neutrophils present in the glomerular capillary lumens.

The visceral epithelial cells showed proliferation in two cases resulting in crescents formations. They were always hypertrophied and contained in their cytoplasm vacuoles with a single limiting membrane. These vacuoles were either empty or filled with more or less electron-dense material. A diffuse fusion of their foot process was rare; most often it was segmental and was always observed in association with subepithelial deposits.

Furthermore, segmental dense deposits of the abnormal substance were seen in all cases on the external side of Bowman's capsule and basement membranes of proximal convoluted tubules. They were also present in the wall of an intertubular capillary in one patient and in the internal elastic lamina of an arteriole in another.

Immunofluorescence microscopy. In the 12 cases studied, bright deposits of C3 were always found in the mesangium although different patterns could be observed. In the usual pattern there were small scattered granules in variable numbers (Fig. 12), but rarely there were clusters of nodules or voluminous masses outlining the mesangial stalk. Deposits of C3 were also found on the glomerular basement membrane, but were weak and of a continuous or discontinuous "linear" pattern (Fig. 12). In four instances, however, basement membrane appeared granular and intensely fluorescent. Deposits of C3 were also observed on segments of variable thickness along Bowman's capsule and tubular basement membranes.

In contrast to these diffuse deposits of C3, there were in most instances no deposits of immunoglobulins C1q, C_4 or properdin.

Results of plasma C3, C1q, C4 and C3 PA measurements

Measurements of plasma *C3 concentrations* were performed in 23 patients (Fig. 13). In five cases, only one

Fig. 11. *MPGN with dense intramembranous deposits: A hump-like deposit is superimposed on a band-like electron-dense deposit which occupies the midportion of the thickened basement membrane (uranyl lead; electron micrograph, × 15,000).* Note the difference of density and granularity of the two kinds of material: very dense and homogeneous in the basement membrane (↗), moderately dense and finely granular in the subepithelial deposit (↗↗).

estimation was done and concentrations were low. Eighteen patients had serial estimations and except for one, all had persistently low concentrations (< 50 mg/100 ml); the last patient had normal concentrations at onset and low C3 concentrations after the second year. In four of these patients, C3 concentrations were studied after transplantation (Pr Crosnier): concentrations were low in two, normal in one and normal for several months before falling to 60 mg/100 ml in the other.

Measurements of plasma *C1q concentrations* were performed in 17 patients (Fig. 14). In six only one estimation was done: the concentrations were normal in five and low in one. Serial estimations were performed in the other 11 patients. Fluctuations occurred in four while seven had normal concentrations.

Measurements of plasma *C4 concentrations* were performed in 20 patients (Fig. 14). In the seven in whom only one estimation was done, the concentrations were normal in all. Serial estimations were done in the other 13 patients. Fluctuations occurred in three while ten always had normal concentrations.

Measurements of plasma *C3 PA concentrations* were

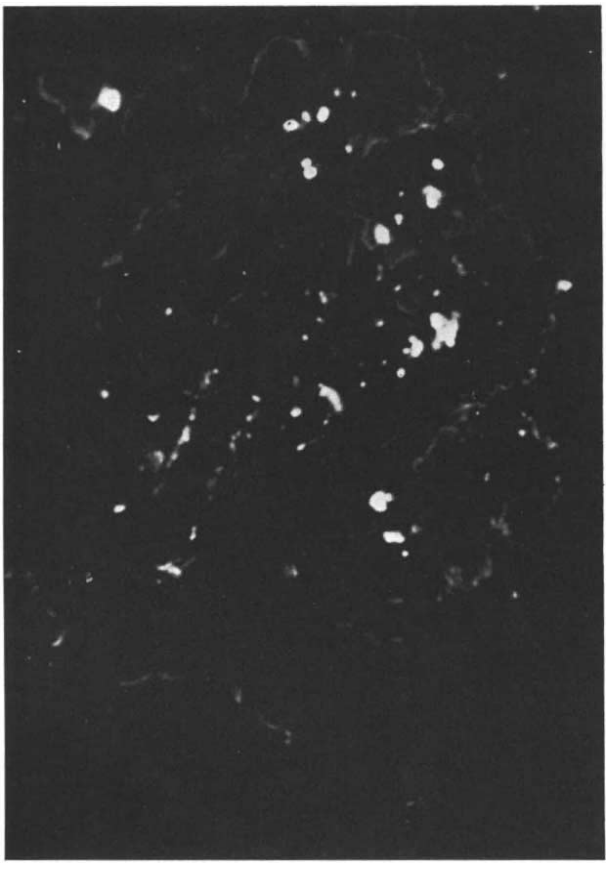

Fig. 12. *MPGN with dense intramembranous deposits: Anti-β_1C globulin (fluorescent microscopy, × 300).* Note weak linear fixation along the capillary basement membranes and the bright granular deposits in the mesangium.

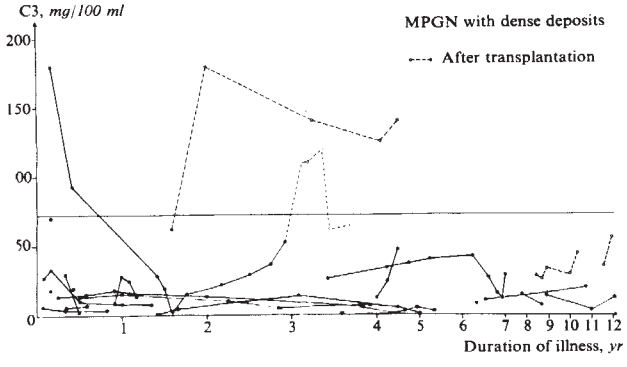

Fig. 13. *Plasma C3 concentrations in MPGN with dense intramembranous deposits at various periods of the disease (23 patients).*

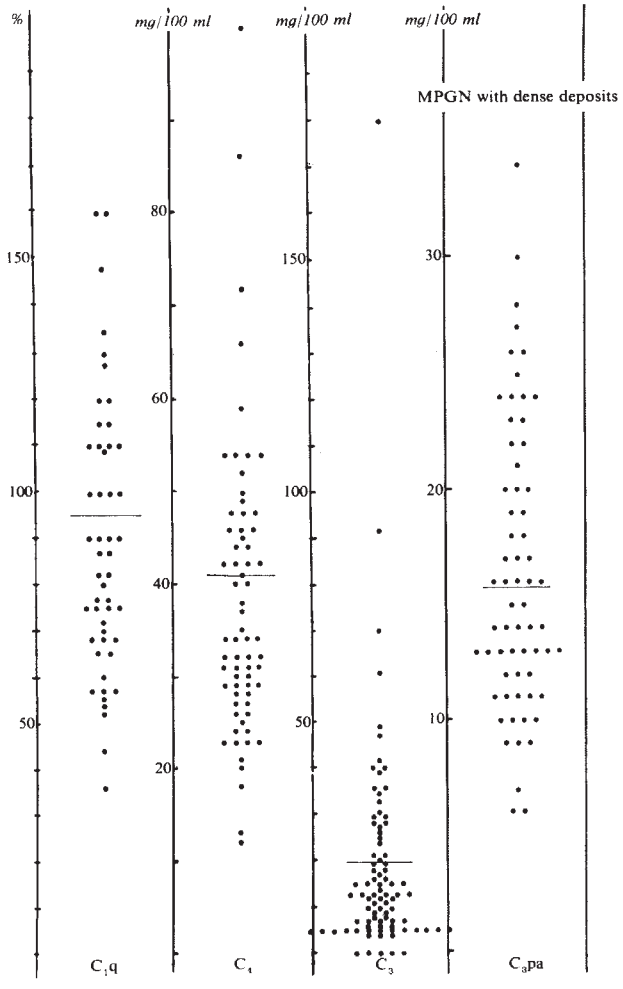

Fig. 14. *Plasma C1q, C4, C3 and C3 PA concentrations in MPGN with dense intramembranous deposits.*

performed in 17 patients (Fig. 14). In the four patients in whom only one estimation was done, the concentrations were normal in two and low in two. Serial estimations were performed in the other 13 patients. Fluctuations occurred in nine while four had normal concentrations.

Discussion

MPGN with dense intramembranous deposits (DIMD) was described as a separate entity by Berger and Galle in 1963 [7], and on several occasions we noted its frequency in children [1, 8, 9]. However, little attention was paid to this condition except in the French literature [10–13]. It was rediscovered by Mathew and Kincaid-Smith in 1971 [14], and since that time several reports have mentioned this anomaly of the basement membrane in some cases of MPGN [15–20].

Although it may closely resemble MPGN with subendothelial deposits (SED) because of the mesangial hypercellularity and the increase in mesangial matrix, MPGN with DIMD can be easily distinguished from it. By light microscopy, using oil immersion and the appropriate stains (trichrome and silver), the basement membrane proper is thickened, refractile and takes on a ribbon-like appearance. By electron microscopy the basement membrane is swollen by an abnormal, strongly electron-dense material located between the epithelial and the endothelial layers, and replacing the lamina densa.

From a clinical point of view, a recent study [5] has shown that clinical presentation and clinical course as well as outcome are similar to those of MPGN with subendothelial deposits. We compared the 44 patients in this study with 88 patients with MPGN and SED who were observed during the same period of time and could not find significant clinical differences between the two groups (Figs. 2 through 5). MPGN with DIMD is rarely discovered by a routine urinalysis (25% vs. 45%), and it often follows a streptococcal infection (20% vs. 11%). Only in this group have we found patients affected with partial lipodystrophy [21–24]. It is usually accompanied by a persistent nephrotic syndrome (55% vs. 42%) and by a macroscopic hematuria (52% vs. 37%). It has apparently a poorer prognosis, since at the end of follow-up, 41% of the patients with DIMD have died of renal insufficiency or are receiving repetitive hemodialysis, while only 25% of the patients with SED have reached the stage of terminal renal failure. This fact is well illustrated by the actuarial survival curves and is mainly due to a greater frequency of association with epithelial crescents (Fig. 6).

Plasma complement [25–27] and immunofluorescence microscopic studies [12, 13, 25, 27] seem, however, to demonstrate special features for each of these varieties of MPGN. *In MPGN with DIMD* the C3 concentrations in the plasma are nearly always constantly very low while the C1q, C4 and C3 PA concentrations may fluctuate but have normal mean levels (Figs. 13 and 14). In contrast, *in MPGN with SED* the levels of C3 are rarely constantly very low. They are most often normal, and when low at onset tend to become normal during the course of the disease. In approximately one-half of the cases, the C1q and C4 concentrations are low or fluctuant and the mean levels are lower than normal. Low or fluctuant levels of C3 PA may be observed as well. In neither of the groups have we been able to establish a correlation between variations in plasma complement components concentrations and the clinical course. Neither the degree of proteinuria nor the occurrence of clinical remissions nor the use of immunosuppressants have an effect on these levels [27].

Immunofluorescence microscopy reveals in all cases of *MPGN with DIMD* the presence of intense granular deposits in the mesangium and of weak "linear" deposits on the basement membranes fixing anti-β_1C serum. There is no deposition of immunoglobulins, early components of complement or properdin. In contrast, in *MPGN with SED* two different patterns are observed: in most cases coarsely granular subendothelial deposits containing β_1C-globulin, immunoglobulins, C1q, C4 and sometimes properdin outline the periphery of the tuft. In some rare cases these granular subendothelial deposits contain only β_1C-globulin and properdin [27].

Therefore, *MPGN with SED* represents a heterogeneous group according to the results of immunofluorescence microscopy and complement studies. In some patients, the presence of immunoglobulins, C1q and C4 associated with β_1C in the glomeruli as well as the finding of reduced plasma C4 concentrations suggest the existence of an activation of the complement sequence by the classical pathway. In this pathway, the activation of complement appears to be induced by immune complexes; however, recruitment of the alternate pathway might occur. In others, the absence of immunoglobulins and of early components of complement, as well as the presence of β_1C globulin and of properdin in the glomeruli, suggests activation of complement by the alternate pathway.

On the other hand, *MPGN with DIMD* represents a homogeneous group in which the characteristic profile of serum complement components (persistently low C3 associated with most often normal C1q, C4 and C3 PA) and the predominant presence of C3 in the glomer-

uli suggest activation of complement through the alternate pathway.

The role of C3 NeF in hypocomplementemic patients is still debated [28]. C3 NeF was present in the serum of two of our patients presenting with lipodystrophy while it was not found in the third patient (Dr. K. Peters). Another surprising fact is the absence of properdin in the glomeruli of our patients, thus suggesting that properdin might not be involved in the activation of complement.

Moreover, the pattern seen by immunofluorescence (weak "linear" deposits of C3 on the basement membrane and coarsely granular in the mesangium) indicates that the characteristic dense material replacing the lamina densa might not represent immune deposits. As suggested by Mahieu [29], this anomaly could be due to a modification of the biochemical composition of the basement membrane. It remains to be determined whether the lesion represents a primary disorder in the basement membrane material with subsequent involvement of the complement system, or a primary disorder of the complement system resulting in a biochemical transformation of the basement membrane.

Another feature of MPGN with DIMD is the constant recurrence of the disease in transplanted kidneys [30], while recurrence has been rarely reported in MPGN with SED [31, 32]. Within a year or so after transplantation, all our patients were found to have dense deposits in their glomerular basement membranes (in the absence of proliferation of mesangial cells) as well as in Bowman's capsule and tubular basement membranes. This factor adds to the specificity of the lesion.

Although there are no significant clinical differences between the two varieties of MPGN, the results of immunopathologic and complement studies seem to imply different pathogenetic mechanisms. MPGN with DIMD may therefore warrant separate classification.

Acknowledgments

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